

**96th Annual Meeting**  
**April 16-20, 2005**  
**Anaheim/Orange County, CA**

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**Abstract Number:** 2045

**Presentation Title:** Genetic identification of glioblastoma maintaining cells in a xenograft model.

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Glioblastoma (GBM) can consist of heterogeneous cell populations. A small CD133+ stem cell-like population has been demonstrated to be responsible for GBM maintenance. We have developed a serial transplantable xenograft GBM model to characterize the genetic background and constitutive signaling pathways in GBM maintaining cells. Freshly isolated GBM cells from a 47-year-old female patient at recurrence were subcutaneously injected into SCID-Beige mice. Xenograft GBM formed in initial SCID-Beige mice were serially transplanted in SCID-Beige or NOD/SCID mice without cell sorting for up to 4 passages. Freshly isolated GBM cells and its xenograft cells at different passages were analyzed for cell surface marker expression. Similar patterns of heterogeneous cell populations were observed both in the GBM and its xenografts at all passages. CD44 and epidermal growth factor receptor were expressed in 90% of the fresh GBM and the xenograft GBM cells. The stem cell marker CD133 was expressed in 70% of the primary GBM and about 30% of the xenograft GBM cells; the platelet-derived growth factor receptor- $\alpha$  (PDGFR $\alpha$ ) in 34% of the primary GBM and about 20% of the xenograft GBM cells. However, the immature neural ganglioside recognized by A2B5 was detected in 63% of the primary GBM but not in the xenograft GBM cells. The same pattern of heterogeneous cell populations was maintained in all passages of xenograft GBM, suggesting that the GBM cell population hierarchy is to a great extent maintained in this xenograft model and that a fraction of GBM cells were capable of maintaining the xenograft GBM by self-renewal. G-band karyotyping showed that the primary GBM cells exhibited great intercellular heterogeneity with a wide variety of related subclones, all of which showed complex karyotypes, including several whole-chromosome losses and unbalanced translocations. In contrast, late passage xenograft cells showed almost no intercellular variation and exhibited a complex karyotype almost identical to one of the original GBM subclones, identified in 3 out of 25 cells in the primary GBM cells. This indicates that the most subclones in the primary GBM did not contribute to the maintenance of xenograft GBM. Interestingly, the PDGFR $\alpha$  expression in the in-vitro cultured xenograft GBM cells was specifically down regulated by a 6-day cyclopamine treatment in a dose-dependent manner. Concomitantly, a 2,5-fold reduction of cell proliferation ( $P < 0,01$ ,  $n = 3$ ) was observed at 10  $\mu$ M cyclopamine treatment. Thus, constitutively active sonic hedgehog signaling critically contributes to GBM cell proliferation via PDGFR $\alpha$  expression in this tumor system. Taken together, our data suggest that even though GBMs consist of heterogeneous cell populations, only a small fraction of these cells is responsible for tumor cell regeneration.

\* The first 2 authors contributed equally to this study.

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